REMARKS

Claims 53-58, 71-73 and 86-95 are pending. Claims 53-58, 88 and 90-94 are amended, and new claim 95 is added. No new matter has been added by the amendments.

Election/Restrictions

The Applicants note the finality of the Restriction Requirement. The Applicants however respectfully request rejoinder of at least the species SEQ ID NOs: 22 and 23 in view of the submissions herein.

Specification

The disclosure is objected to for containing an embedded hyperlink and/or other form of browser-executable code at p. 54-55. In response, the paragraph spanning p. 54-55 has been amended to remove the browser-executable code.

Rejections Under 35 U.S.C. § 112

I. Claims 53-58, 71-73 and 86-94 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. More specifically, while the Examiner acknowledges that the specification describes an actual reduction to practice of SEQ ID NO: 24, the Examiner asserts that the claims are drawn to a large genus of variants of SEQ ID NO: 24, and that the Applicants were allegedly not in possession of this genus with respect to fragments or variants or substantially identical sequences.

Claims 53-55, which are the only pending independent claims, have been amended without prejudice or disclaimer and without acquiescence to the Examiner's assertions, to recite that the claimed polypeptide comprises an amino acid sequence having at least 75% sequence identity to SEQ ID NO: 24 and to recite an "immunogenic fragment." Support for these amendments may be found throughout the specification at for example page 13, lines 6-28; page 18, line 26 to page 19, line 6; or page 30, line 12, to page 31, line 23. The Applicants respectfully submit that the specification describes at least three variants of SEQ ID NO: 24, *i.e.*, NleA

polypeptides from enteropathogenic *E. coli* (EPEC) and from *C. rodentium*, as well as from enterohemorrhagic *E. coli* (EHEC), which fall within the presently claimed sequence identity, and therefore describes a representative number of species with respect to the claimed genus. Furthermore, recitation of an "immunogenic fragment" clarifies that only fragments capable of eliciting an immune response are contemplated. Accordingly, this rejection should be withdrawn.

II. Claims 53-58, 71-73 and 86-94 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. More specifically, while the Examiner acknowledges that the specification is enabling for a method for eliciting an immune response against an enterohemorrhagic *E. coli* (EHEC) or SEQ ID NO: 24 (which is characterized as a component of enterohemorrhagic *E. coli* O157:H7), or for reducing colonization or shedding of EHEC, or for treating EHEC infection, in an animal by administering an effective amount of a composition or cell culture supernatant including a polypeptide which comprises the amino acid sequence set forth in SEQ ID NO: 24, the Examiner alleges that other aspects of the claimed invention are not enabled. In particular, the Examiner alleges that the specification does not reasonably provide enablement for preventing infection by EHEC in an animal by administering an effective amount of a composition or cell culture supernatant including a polypeptide which comprises the amino acid sequence set forth in SEQ ID NO: 24. The Examiner also alleges that the specification does not reasonably provide enablement for the claimed methods with respect to any other A/E pathogen, or component thereof, or for another polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NO: 24 or a fragment or variant thereof.

Claims 53-55, which are the only pending independent claims, have been amended without prejudice or disclaimer and without acquiescence to the Examiner's assertions, to recite that the claimed polypeptide comprises an amino acid sequence having at least 75% sequence identity to SEQ ID NO: 24 and to recite an "immunogenic fragment." In addition, the present claims do not recite prevention of infection.

As indicated herein, the specification describes at least three variants of SEQ ID NO: 24,

i.e., NleA polypeptides from EPEC and from *C. rodentium* and therefore describes a representative number of species with respect to the claimed genus. Furthermore, one of ordinary skill in the art would also be able to readily identify NleA variants as, for example, evidenced in the enclosed publication by Creuzburg and Schmidt (J. Clin. Microbiol. 2498-2507, 2007) in which a large number of NleA variants were detected after the initial identification of NleA as a virulence factor by the inventors of the above-referenced application.

The Applicants also respectfully submit that the specification demonstrates the effect of NleA in a *C. rodentium* mouse model of disease and that one of ordinary skill in the art would be able to readily apply the claimed methods to A/E pathogens, as claimed. Accordingly, one of ordinary skill in the art would be able to readily identify variants and immunogenic fragments of NleA proteins, and to use the claimed methods in connection with A/E pathogens, and the Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102

I. Claims 53-58, 71-72 and 86-94 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Finlay *et al.* (WO 02/053181) as evidenced by Hideo *et al.* (JP20023550742A2, partial translation and sequence alignment attached as Appendix B and Appendix A, respectively, of the Office Action).

More specifically, the Examiner alleges that Finlay *et al.* teach methods for eliciting an immune response against an A/E pathogen or component thereof, or for reducing colonization of an A/E pathogen, or of reducing shedding (thus allegedly treating an infection by an A/E pathogen) in an animal by administering an effective amount of a composition comprising a culture supernatant. The Examiner further alleges that Hideo *et al.* teach that *E. coli* EHEC O157:H7 makes a protein comprising the sequence of SEQ ID NO: 24. The Office Action further alleges that the culture supernatant of Finlay *et al.* is prepared from *E. coli* EHEC O157:H7 under identical conditions as SEQ ID NO: 24 of the instant specification.

The Examiner therefore concludes that the culture supernatant of Finlay *et al.* is a composition or culture supernatant which comprises a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NO: 24 and inherently

comprises 20% of the cell protein present in the composition. The Examiner is respectfully requested to clarify "inherently comprises 20% of the cell protein present in the composition" in the context of this rejection.

To support a rejection under § 102, a single prior art reference must describe each and every element, either expressly or inherently, of the rejected claims (MPEP § 2131). In the present case, claims 53-55, which are the only pending independent claims, have been amended without prejudice or disclaimer and without acquiescence to the Examiner's assertions, to recite that the claimed polypeptide is "isolated." The term "isolated" as defined in the specification refers to a compound that is "separated from the components that naturally accompany it" (see, for example, the specification at page 10, lines 20-21). The Applicants respectfully submit that Finlay *et al.* do not teach methods relating to an "isolated" polypeptide comprising an amino acid sequence having at least 75% sequence identity to the sequence of SEQ ID NO: 24 as claimed and therefore do not anticipate the claimed invention.

II. Claims 53-58, 71-72, 86, and 88-94 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Wright (US 5,730,989, 3/24/98) as evidenced by Hideo *et al.* (*supra*).

More specifically, the Examiner alleges that Wright disclose a method for eliciting an immune response against *E. coli* O157:H7 or component thereof, in an animal by administering to the animal an effective amount of inactivated *E. coli* O157:H7. The Examiner further alleges that the *E. coli* O157:H7 of Wright is a composition that comprises a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, as evidenced by Hideo *et al.*, and that Wright disclose a method for treating *E. coli* infection, thus treatment of the *E. coli* infection will allegedly result in reduction in colonization and shedding of *E. coli* in an animal.

As indicated herein, to support a rejection under § 102, a single prior art reference must describe each and every element, either expressly or inherently, of the rejected claims (MPEP § 2131). In the present case, claims 53-55, which are the only pending independent claims, have been amended without prejudice or disclaimer and without acquiescence to the Examiner's assertions, to recite that the claimed polypeptide is "isolated." The Applicants respectfully

submit that Wright *et al.* do not teach methods relating to use of an "isolated" polypeptide comprising an amino acid sequence having at least 75% sequence identity to the sequence of SEQ ID NO: 24 as claimed and therefore do not anticipate the claimed invention.

III. Claims 53-55, 71-72, 86 and 90 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Hideo *et al.* (*supra*) as evidenced by Wright *et al.* (*supra*).

More specifically, the Examiner alleges that Hideo *et al.* disclose a method of eliciting an immune response against *E. coli* O157:H7 by administering an effective amount of a composition for inducing an immune response against *E. coli* O157:H7 comprising a protein 100% identical to SEQ ID NO: 24. The Examiner further alleges that Hideo *et al.* also disclose treating an infection by *E. coli* O157:H7 using the composition and concludes that treatment of the *E. coli* infection will result in reduction in colonization and shedding of *E. coli* in an animal. The Examiner further alleges that it is inherent that the methods of Hideo *et al.* are to be practiced in animals since Wright *et al.* teach that *E. coli* O157:H7 infects animals.

This rejection is respectfully traversed. As indicated herein, claims 53-55 are the only pending independent claims, and therefore these rejections will be addressed with respect to these claims only. The remaining claims at issue under these rejections are dependent claims and by definition subject to the limitations of claims 53, 54 or 55. Claims 53-55 are directed to methods for eliciting an immune response against an A/E pathogen or component thereof, or for reducing colonization or shedding of an A/E pathogen, in an animal by administering an effective amount of a composition or culture supernatant including an isolated polypeptide comprising an amino acid sequence having at least 75% sequence identity to the sequence of SEQ ID NO: 24.

The Applicants reiterate that, to support a rejection under § 102, a single prior art reference must describe each and every element, either expressly or inherently, of the rejected claims (MPEP § 2131) and the prior art reference must be enabling:

> "...invalidity based on anticipation requires that the assertedly anticipating disclosure enable the subject matter of the reference and thus of the patented invention without undue experimentation." *Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education & Research*, 346 F.3d 1051, 68 USPQ2d 1372 (Fed. Cir. 2003), hereafter

"*Elan*," emphasis added.

Hideo *et al.* do not meet these requirements, as discussed herein.

Hideo *et al.* teach nucleotide sequences from enterohemorrhagic *E. coli* O157:H7 SAKAI (referred to hereafter as the "EHEC sequences") and assert that these sequences are not present in non-pathogenic *E. coli* K12 (see page 40, paragraph [0010], and page 71, paragraph [0014], of the enclosed English translation of Hideo *et al.*). Hideo *et al.* also teach predicted amino acid sequences based on the identified nucleotide sequences and comparison of the amino acid sequences to known sequences from various public databases using known algorithms (see page 71, paragraph [0016] of the enclosed English translation of Hideo *et al.*). Hideo *et al.* classify the predicted amino acid sequences into twelve (12) groups (see pages 71-72, paragraph [0017] of the enclosed English translation of Hideo *et al.*), as follows: 1) Proteins having unknown function etc., 2) Proteins which have unknown function, but have significant homology to that of other bacteria, 3) Proteins comprising Insertion Sequences (IS), 4) Proteins derived from phage, 5) Regulatory elements, 6) Proteins relating to fimbriae, 7) Proteins relating to transportation of substance, 8) Proteins relating to synthesis of lipopolysaccharide, 9) Proteins relating to metabolism, 10) Proteins processing DNA/RNA, 11) Proteins relating to pathogenicity, and 12) Other proteins.

Hideo *et al.* also teach that:

> …a protein predicted to be a cell surface protein (membrane protein, especially, OMP, lipoprotein) in them or its gene (or nucleic-acid molecule) may be useful for production of an antibody, vaccine composition, diagnosis of O-157 infection and the like. Furthermore, there is a possibility that they include a protein which has an important function in O-157, for example, transportation and metabolism of a substance, processing of nucleic acids, and relates to a regulatory element and pathogenicity. They are to be useful for diagnosis and therapy of O-157 infection." (see pages 267-270, paragraph [0031] of the enclosed English translation of Hideo *et al.*, emphasis added)
> …
>
> O-157 specific nucleic-acid molecule of the present invention, a gene included in it, peptide and nucleic-acid sequence encoded by the gene are useful for diagnosis and/or therapy of O-157 infection and prevention of symptom occurred by the infection. They can also be used for detection of the presence of O-157 in a sample and classification of its strain. Furthermore, they can also be used for screening of useful compounds for

> prevention and/or therapy of O-157 infection and symptom occurred by the infection. (see page 283, paragraph [0047] of the enclosed English translation of Hideo *et al.*, emphasis added)
>
> ...
>
> the scope of the present invention includes a vaccine composition including genes and/or polynucleotides of the present invention, and a method for prevention and/or therapy of O-157 infection and symptom occurred by the infection. (see page 283, paragraph [0048] of the enclosed English translation of Hideo *et al.*, emphasis added)
>
> ...
>
> The present invention relates to a peptide vaccine formulation for prevention or therapy of O-157 infection comprising effective amount of, at least one kind of, O-157 specific polypeptides having amino acid sequence set forth in the sequence lists or fragments thereof. The vaccine formulation preferably includes a pharmaceutically acceptable carrier, for example, a known adjuvant in the art. (see page 284, paragraph [0051] of the enclosed English translation of Hideo *et al.*, emphasis added).
>
> ...
>
> The present invention relates to a method of reducing the risk of O-157 infection in patients or a method for therapy [of the infection]. This method comprises administration of the vaccine formulation of the present invention to a patient so as to reduce the risk of O-157 infection or provide therapy of infection.(see page 285, paragraph [0053] of the enclosed English translation of Hideo *et al.*, emphasis added).

The Applicants respectfully submit that these teachings of Hideo *et al.* do not rise to the level of anticipation of the claimed invention. Firstly, SEQ ID NO: 393 of Hideo *et al.*, which is asserted to be identical to SEQ ID NO: 24 of the instant application, is called out in Group 2 (Proteins which have unknown function, but have significant homology to that of other bacteria) and is described as follows at page 154 of the enclosed English translation of Hideo *et al.*:

> SEQ ID NO: 393 -0.239229, 442, a minor capsid protein precursor, similar to minor capsid protein precursors for example ,GpC [Bacteriophage lambda] gi|137565|sp|P03711|VCAC#LAMBD (97% identity in 439 amino acids), capsid assembly protein containing Nu3-homolog;

The Applicants respectfully note that Hideo *et al.* do not identify SEQ ID NO: 393 as relating to pathogenicity – such sequences are listed in Group 11. The Applicants respectfully submit that capsid proteins are bacteriophage (bacterial virus) proteins used as part of the viral assembly process, and present in the viral coat upon maturation. Accordingly, a bacteriophage

capsid protein would not be expected to be effective in the methods as claimed.

Secondly, Hideo *et al.* speculate that a protein that is "predicted to be a cell surface protein … may be useful for production of an antibody, vaccine composition, diagnosis of O-157 infection …," that "… there is a possibility that they include a protein which has an important function in O-157, for example, transportation and metabolism of a substance, processing of nucleic acids, and relates to a regulatory element and pathogenicity..." and that such proteins "… are to be useful for diagnosis and therapy of O-157 infection."

Accordingly, Hideo *et al.* simply raise the possibility that some of approximately two thousand (2000) sequences may be useful. This assumption appears to be based on the absence of the EHEC sequences from *E. coli* K12. Hideo *et al.* compare the sequence of the pathogenic bacterium, EHEC O157:H7, with that of the non-pathogenic K12 strain, and assert that the EHEC O157:H7 sequences that differ from the K12 sequences are pathogenic simply because EHEC O157:H7 is highly pathogenic and K12 is not. Hideo *et al.* do not provide any experimental data or other evidence to support this assertion.

The Applicants respectfully submit that the assumption that any sequence present in a pathogenic organism and absent from a non-pathogenic organism is necessarily useful is incorrect and that very few of the EHEC O157:H7-specific sequences are implicated in human disease. More specifically, non-pathogenic K12 and EHEC O157:H7 share about 80% sequence identity and are about 20% different. Given that the genomes of these organisms are about 4 million base pairs, the difference is about 800,000 base pairs. All the known virulence factors encode only about 50-100,000 base pairs (*e.g.,* the LEE region, which encodes the Type III secretion system is 34,000 base pairs, the Shiga toxin is 1,000 base pairs, *etc.*), thus making up only a small fraction of genomic differences between non-pathogenic K12 and pathogenic EHEC O157:H7. For example, many of the non-LEE encoded proteins have no effect on virulence, and are found in O157 but not in non-pathogenic *E. coli*. Accordingly, one of ordinary skill in the art would recognize that not all of the EHEC O157:H7-specific sequences set out in Hideo *et al.* encode virulence factors. Furthermore, the inventors of the present application were the first to identify NleA polypeptide (SEQ ID NOs: 22-24) as a virulence factor. The term "virulence

factor" is understood by those of skill in the art as a molecule required to cause disease, that is not normally required for viability of the micro-organism producing it in non-disease settings. It is further well known to a skilled person that, once identified, a virulence factor is useful to induce an immune response in animals, but prior to such identification there would be no reason to conclude that any protein would be useful.

Furthermore, Hideo *et al.* make it clear that the contemplated use of the disclosed sequences is in the context of treating infection in a patient. The term "infection" is defined as "[i]nvasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms" or the "pathological state resulting from having been infected." (see, infection, Dictionary.com, *The American Heritage® Stedman's Medical Dictionary*. Houghton Mifflin Company. http://dictionary.reference.com/browse/infection, accessed: November 18, 2010). Therefore, the term "infection" contemplates that the infected subject or animal exhibits symptoms of clinical disease. By contrast, ruminants may be colonized by and shed highly virulent A/E pathogens, or exhibit an immune response against an A/E pathogen or component thereof, without ever exhibiting symptoms of overt disease.

Accordingly, the Applicants respectfully submit that Hideo *et al.* do not teach methods relating to use of an isolated polypeptide comprising an amino acid sequence having at least 75% sequence identity to the sequence of SEQ ID NO: 24 in ruminants, as claimed, and therefore do not anticipate the claimed invention.

For the sake of completeness, the Applicants note that the Examiner also asserts that Wright *et al.* teach that *E. coli* O157:H7 infects animals. With respect, Wright *et al.* disclose that *E. coli* O157:H7 "was the first EHEC strain identified in humans and remains the most common infectious cause of bloody diarrhea and hemorrhagic colitis in humans" (col. 1, ll. 34-36, emphasis added). Wright *et al.* also disclose that "...cattle, pigs, lambs and poultry may all be environmental reservoirs for verocytotoxin-producing enterohemorrhagic *E. coli*" (col. 1, ll. 49-51, emphasis added). The term "reservoir" is defined as "[a]n organism or a population that directly or indirectly transmits a pathogen while being virtually immune to its effects" (see,

reservoir, Dictionary.com, *The American Heritage® Stedman's Medical Dictionary*. Houghton Mifflin Company. http://dictionary.reference.com/browse/infection, accessed: November 18, 2010). Accordingly, the Examiner is in error in stating that Wright *et al*. teach that *E. coli* O157:H7 infects animals since the term "infection" contemplates that the infected subject or animal exhibits symptoms of clinical disease.

Rejections Under 35 U.S.C. § 103

Claims 53-58, 71-72, 86 and 90-94 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Hideo *et al*. (*supra*) in view of Wright *et al*. (*supra*).

More specifically, the Examiner alleges that Hideo *et al*. disclose a method of eliciting an immune response against *E. coli* O157:H7 by administering an effective amount of a composition for inducing an immune response against *E. coli* O157:H7 comprising a protein identical to SEQ ID NO: 24. The Examiner further alleges that Hideo *et al*. also disclose treating an infection by *E. coli* O157:H7 using the composition. The Examiner further alleges that treatment of the *E. coli* infection will result in reduction in colonization and shedding of *E. coli* in an animal. While the Examiner concedes that Hideo *et al*. do not disclose that the animal is a ruminant or bovine or ovine or human, the Examiner alleges that it is inherent that the methods of Hideo *et al*. are to be practiced in animals since Wright *et al*. teach that *E. coli* or *E. coli* O157:H7 infect animals, such as cattle, lamb and humans and causes diarrhea.

The Examiner therefore alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to have used the method of Hideo *et al*. for animals such as cattle, lamb and humans, thus resulting in the instant invention with a reasonable expectation of success. The Examiner finds the motivation to do so in the teachings of Wright *et al*. that *E. coli* or *E. coli* O157:H7 infect cattle, lamb and humans and cause diarrhea.

This rejection is respectfully traversed. The Applicants respectfully submit that, further to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of

the Supreme Court Decision in KSR International Co. v. Teleflex Inc. (72 Fed. Reg. 57,526 (Oct. 10, 2007); hereafter the "Guidelines"), a proper rejection under 35 U.S.C. § 103 requires:

1. a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

2. a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;

3. a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

4. whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

In the present case, as discussed herein, the teachings of Hideo *et al.* are speculative and the teachings of Wright *et al.* do not cure the defect in Hideo *et al.*

More specifically, Hideo *et al.* compare the sequence of the pathogenic bacterium, EHEC O157:H7, with that of the non-pathogenic K12 strain, and speculate that the approximately 2000 EHEC O157:H7 sequences that differ from the K12 sequences are pathogenic simply because EHEC O157:H7 is highly pathogenic and K12 is not. For example, Hideo *et al.* speculate that a protein that is "predicted to be a cell surface protein … may be useful for production of an antibody, vaccine composition, diagnosis of O-157 infection …," that "… there is a possibility that they include a protein which has an important function in O-157, for example, transportation and metabolism of a substance, processing of nucleic acids, and relates to a regulatory element

and pathogenicity..." and that such proteins "... are to be useful for diagnosis and therapy of O-157 infection." Hideo *et al.* do not provide any experimental data or other evidence to support these speculations.

As is discussed in detail above, the assumptions made by Hideo *et al.* are incorrect and very few of the EHEC O157:H7-specific sequences are implicated in human disease. Accordingly, one of ordinary skill in the art would recognize that not all of the EHEC O157:H7-specific sequences set out in Hideo *et al.* encode virulence factors.

Furthermore, SEQ ID NO: 393 of Hideo *et al.*, which is asserted to be identical to SEQ ID NO: 24 of the instant application, is identified as being of unknown function but similar to a capsid protein, which are bacteriophage (bacterial virus) proteins used as part of the viral assembly process and would not be expected to be effective in the methods claimed in the instant application. As discussed above, the inventors of the present application were the first to identify NleA polypeptide (SEQ ID NOs: 22-24) as a virulence factor, which would then lead a skilled person to conclude that it would be useful to induce an immune response. Prior to such identification there would be no reason to conclude that any protein would be useful in the methods claimed in the instant application.

Finally, Hideo *et al.* make it clear that the contemplated use of the disclosed sequences is in the context of treating infection in a patient rather than in ruminants, which may be colonized by and shed highly virulent A/E pathogens, or exhibit an immune response against an A/E pathogen or component thereof, without ever exhibiting symptoms of overt disease.

Turning to Wright *et al.*, this reference discloses that *E. coli* O157:H7 "was the first EHEC strain identified in humans and remains the most common infectious cause of bloody diarrhea and hemorrhagic colitis in humans" (col. 1, ll. 34-36, emphasis added). Wright *et al.* also disclose that "...cattle, pigs, lambs and poultry may all be environmental reservoirs for verocytotoxin-producing enterohemorrhagic *E. coli*" (col. 1, ll. 49-51, emphasis added). The term "reservoir" is defined as "[a]n organism or a population that directly or indirectly transmits a pathogen while being virtually immune to its effects" (see, reservoir, Dictionary.com, *The American Heritage® Stedman's Medical Dictionary*. Houghton Mifflin Company.

http://dictionary.reference.com/browse/infection, accessed: November 18, 2010). Therefore, contrary to the Examiner's assertion, Wright *et al.* do not teach that *E. coli* O157:H7 infects ruminants since the term "infection," as indicated herein, contemplates that the infected subject or animal exhibits symptoms of clinical disease.

Accordingly, one of ordinary skill in the art would not have recognized that the results of the combination of Hideo *et al.* and Wright *et al.* were predictable since Hideo *et al.* provide no guidance as to which of over 2000 sequences may be useful and Wright *et al.* do not cure this defect. Therefore, Hideo *et al.*, considered alone or in combination with Wright *et al.*, do not render the claimed invention obvious.

Claims 53-55, 71-72, 86, 88-89 and 90 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Hideo *et al.* (*supra*) as evidenced by Wright *et al.* (*supra*) in view of Finlay *et al.* (*supra*).

More specifically, the Office Action alleges that Hideo *et al.* disclose a method of eliciting an immune response against *E. coli* O157:H7 by administering an effective amount of a composition for inducing an immune response against *E. coli* O157:H7 comprising a protein identical to SEQ ID NO: 24. The Office Action further alleges that Hideo *et al.* also disclose treating an infection by *E. coli* O157:H7 using the composition. The Office Action further alleges that treatment of the *E. coli* infection will result in reduction in colonization and shedding of *E. coli* in an animal. The Office Action further alleges that it is inherent that the methods of Hideo *et al.* are to be practiced in animals since Wright *et al.* teach that *E. coli* or *E. coli* O157:H7 infect animals.

While the Office Action concedes that Hideo *et al.* do not disclose that the composition further comprises EspA, EspB, EspD, EspC, intimin and Tir or an adjuvant, the Office Action alleges that Finlay *et al.* teach methods for eliciting an immune response against an A/E pathogen or component thereof, or for reducing colonization of an A/E pathogen, or of reducing shedding (thus allegedly treating an infection by an A/E pathogen) in an animal by administering an effective amount of a composition comprising a culture supernatant where the composition includes EspA, EspB, EspD, EspC, intimin and Tir and/or further includes an adjuvant. The

Office Action further alleges that Finlay *et al.* teach that the composition treats the EHEC infection and/or reduces colonization of the animal and teach that administration of the composition to an animal stimulates an immune response against one or more secreted antigens, such as EspA and Tir, which blocks attachment of the EHEC to intestinal epithelial cells.

The Office Action therefore alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to have combined the composition of Hideo *et al.* with that of Finlay *et al.*, thus resulting in the instant method (wherein the composition further comprises EspA, EspB, EspD, EspC, intimin and Tir or further comprises an adjuvant) with a reasonable expectation of success. The Office Action finds the motivation to do so because both compositions are allegedly individually taught in the prior art to be useful for the same purpose *i.e.*, inducing an immune response against *E. coli* EHEC O157:H7 and Finlay *et al.* allegedly provide additional motivation in that administration of the composition to an animal stimulates an immune response against one or more secreted antigens, such as EspA and Tir, that blocks attachment of the EHEC to intestinal epithelial cells.

This rejection is respectfully traversed. As discussed herein, in the sections addressing the rejections under 35 U.S.C. 102(b) and 103(a) with respect to Hideo *et al.*, one of ordinary skill in the art would not have recognized that the results of the combination of Hideo *et al.* and Wright *et al.*, with or without Finlay *et al.*, were predictable since Hideo *et al.* provide no guidance as to which of approximately two thousand (2000) sequences may be useful and Wright *et al.* do not cure this defect. The addition of Finlay *et al.* also does not cure the defects in Hideo *et al.* and Wright *et al.* More specifically, as indicated herein, the inventors of the present application were the first to identify NleA polypeptide (SEQ ID NOs: 22-24) as a virulence factor, which would then lead a skilled person to conclude that it would be useful to induce an immune response. Prior to such identification there would be no reason to conclude that any protein would be useful in the methods claimed in the instant application and Finlay *et al.* do not provide such identification. Accordingly Hideo *et al.*, considered alone or in combination with Wright *et al.* and/or Finlay *et al.*, do not render the claimed invention obvious.

Conclusion

The Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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